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Malignant pleural mesothelioma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

Malignant pleural mesothelioma (MPM) is a rare tumor. The incidence is 1.25/100 000 in Great Britain and 1.1/100 000 in Germany. Within the next 20 years the incidence is estimated to double in many countries. Exposure to asbestos is a well-established etiological factor for MPM, with occupational exposure having been documented in 70–80% of those affected.

diagnosis

Patients typically present with shortness of breath due to pleural effusion or chest pain in a more advanced stage. The diagnosis is usually suggested by imaging studies (unilateral pleural thickening; pleural effusion). An occupational history must be obtained.

Cytological examination of the effusion can be diagnostic, but often shows equivocal results. Therefore, histology is the gold standard. Video-assisted thoracoscopy or open pleural biopsy in a fused pleural space may be needed to provide sufficient material for accurate histological diagnosis. There are three main histological types (epithelial, sarcomatous and mixed) with ~60% being epithelial.

Recent data suggest the possible contribution of serum mesothelin-related proteins and osteopontin as useful markers to support the diagnosis of mesothelioma, although the precise role of these markers is yet to be defined.

staging and risk assessment

Accurate initial staging is essential to provide both prognostic information and guidance on the most appropriate therapeutic options. Clinical staging is based on a CT scan of the chest. However, the conversion of such images into TNM stages is often inconclusive. Mediastinoscopy and video-assisted thoracoscopy may be useful in determining stage. The international staging system for MPM emphasizes the extent of disease post surgery in a traditional TNM system and stratifies patients into similar prognostic categories as shown in Table 1.

The Cancer and Leukemia Group B and the European Organization for Research and Treatment of Cancer prognostic scores may be used. They include performance status, age, histological type, weight loss and white blood count.

MPM rarely metastasizes to distant sites but most patients present with locally advanced disease. The use of PET scan to rule out extra thoracic metastasis is under investigation and findings seem promising.

treatment

surgery

Different surgical procedures have been tested with varying degrees of success.

Extra-pleural pneumonectomy (EPP) with resection of the hemi-diaphragm and the pericardium *en bloc* has the potential to be a radical treatment and this approach is generally

Table 1.

Stage	TNM	Comments
Ia	T1a N0 M0	Primary tumor limited to ipsilateral parietal pleura
Ib	T1b N0 M0	As stage Ia plus focal involvement of visceral pleura
II	T2 N0 M0	As stage Ia or Ib plus confluent involvement of diaphragm or visceral pleura or involvement of the lung
III	any T3 M0	Locally advanced, potentially resectable tumor
	any N1 M0	Ipsilateral, bronchopulmonary or hilar lymph node involvement
	any N2 M0	Subcarinal or ipsilateral mediastinal lymph node involvement
IV	any T4	Locally advanced technically unresectable tumor
	any N3	Contralateral mediastinal, internal mammary, and ipsilateral or contralateral supraclavicular lymph node involvement
	any M1	Distant metastases

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combined with chemotherapy and/or adjuvant radiotherapy. Surgery, the appropriateness of which is still under consideration, should only be performed on selected patients by experienced thoracic surgeons in the context of a multidisciplinary team [III, A]. Selection criteria for EPP include good ECOG performance status, early-stage disease without mediastinal lymph node involvement, epithelial histology and adequate pulmonary function to withstand a pneumonectomy. Pleurectomy/decortication may be indicated in early stages or when EPP would leave macroscopic tumor behind.

Local palliative procedures to control pleural effusion include parietal pleurectomy or talc pleurodesis.

radiotherapy

The use of hemithoracic radiotherapy is limited because of the severe side-effects of irradiation of the underlying lung. Conventional radiotherapy doses can be delivered locally as a palliative measure for pain management. Modern radiotherapy techniques allow for delivering high-dose radiotherapy in an attempt to improve local control after EPP. Prophylactic radiotherapy to reduce the incidence of port metastases is controversial and not routinely applied.

chemotherapy

Platinum analogs, doxorubicin and some antimetabolites (raltitrexed, pemetrexed) have shown modest single-agent activity [III, B].

The combinations of both pemetrexed/cisplatin and raltitrexed/cisplatin have been shown to improve survival as well as lung function and symptom control in comparison with cisplatin alone in randomized trials [II, A].

In a phase III trial examining second-line pemetrexed versus best supportive care, a longer time to disease progression was seen in the chemotherapy arm with no difference in overall survival.

If EPP is planned, neoadjuvant or adjuvant chemotherapy should be considered.

response evaluation

Response evaluation using CT scan is recommended after two to three chemotherapy cycles and the modified RECIST criteria should be applied.

follow-up

Follow-up consists of clinical evaluation with particular attention to symptoms or chest wall recurrence and chest CT as needed.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

literature

1. Peto J, Decarli A, La Vecchia C et al. The European mesothelioma epidemic. Br J Cancer 1999; 86: 1970–1971.
2. Pelucchi C, Malvezzi M, La Vecchia C et al. The mesothelioma epidemic in Western Europe: an update. Br J Cancer 2004; 90: 1022–1024.
3. Robinson BW, Creaney J, Lake R et al. Mesothelin-family proteins and diagnosis of mesothelioma. Lancet 2003; 362: 1612–1616.
4. Sugarbaker DJ, Flores RM, Jaklitsch MT et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg 1999; 17: 54–63.
5. Waller DA. The role of surgery in diagnosis and treatment of malignant pleural mesothelioma. Curr Opin Oncol 2003; 15: 139–143.
6. Weder W, Stahel RA, Bernhard J et al. Multicenter trial of neoadjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. Ann Oncol 2007; 18: 1196–1202.
7. Rice DC, Smythe WR, Liao Z et al. Dose-dependent pulmonary toxicity after postoperative intensity-modulated radiotherapy for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2007; 69: 350–357.
8. O'Rourke N, Garcia JC, Paul J et al. A randomized controlled trial of intervention site radiotherapy in malignant pleural mesothelioma. Radiother Oncol 2007; 84: 18–22.
9. Ellis P, Davies AM, Evans WK et al. The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a systematic review and practice guideline. J Thorac Oncol 2006; 1: 591–601.
10. Steele JP, Klabatsa A. Chemotherapy options and new advances in malignant mesothelioma. Ann Oncol 2005; 16: 345–351.
11. Vogelzang NJ, Rusthoven JJ, Symanowski J et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003; 21: 2636–2644.
12. van Meerbeeck JP, Gaafar R, Manegold C et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol 2005; 23: 6881–6889.
13. Bottomley A, Gaafar R, Manegold C et al. Short-term treatment-related symptoms and quality of life: results from an international randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an EORTC Lung-Cancer Group and Natioanl Cancer Institute, Canada. Intergroup Study. J Clin Oncol 2006; 24: 1435–1442.
14. Jassem J, Ramlau R, Santoro A et al. A randomised phase III trial comparing pemetrexed plus best supportive care vs best supportive care in previously treated patients with advanced malignant mesothelioma. Ann Oncol 2006; 17 (Suppl 9): Abstr 7150.
15. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol 2004; 15: 257–260.